(FILE 'HOME' ENTERED AT 22:27:51 ON 21 FEB 2001)

FILE 'CAPLUS, MEDLINE, USPATFULL' ENTERED AT 22:28:14 ON 21 FEB 2001

L1	1004	S	TITIN
L2	284	S	L1 AND (HEART OR CARDIAC OR CARDIO?)
L3	175		DUPLICATE REMOVE L2 (109 DUPLICATES REMOVED)
L4	12	S	L3 AND MUTATION
L5	0	S	L4 AND PICKWICK
L6	0	S	L3 AND PICKWICK
L7	0	S	L3 AND N2B EXON
L8	12	S	L3 AND (MUTATION OR ABERRANT OR ABERRENT OR POLYMORPHISM)
L9	0	S	L3 AND ZEBRAFISH

L8 ANSWER 1 OF 12 CAPLUS COPYRIGHT 2001 ACS
AN 2000:375288 CAPLUS
DN 133:15444
TI Genetic alteration in **cardiomyopathy**
AU Kimura, Akinori
CS Res. Inst. Instractable Dis., Tokyo Med. Dent. Univ., Japan
SO Byori to Rinsho (2000), 18(6), 541-547
CODEN: BYRIEM; ISSN: 0287-3745
PB Bunkodo
DT Journal; General Review
LA Japanese
AB A review with 18 refs., on the mutations in genes for sarcomere proteins (**cardiac** .beta.-myosin heavy chain, **cardiac** troponin T, .alpha.-tropomyosin, **titin**, etc.) in hypertrophic **cardiomyopathy** (HCM), relationship between these genetic alterations and prognosis of HCM, and mutations in genes for **cardiac** .alpha.-actin, desmin, laminin A/C, and dystrophin in dilated **cardiomyopathy** and other types of idiopathic **cardiomyopathy**.

L8 ANSWER 2 OF 12 CAPLUS COPYRIGHT 2001 ACS
AN 1999:707307 CAPLUS
DN 132:34094
TI Dilated **cardiomyopathy** in homozygous myosin-binding protein-C mutant mice
AU McConnell, Bradley K.; Jones, Karen A.; Fatkin, Diane; Arroyo, Luis H.; Lee, Richard T.; Aristizabal, Orlando; Turnbull, Daniel H.; Georgakopoulos, Dimitrios; Kass, David; Bond, Meredith; Niimura, Hideshi; Schoen, Frederick J.; Conner, David; Fischman, Donald H.; Seidman, Christine E.; Seidman, J. G.
CS Department of Genetics, Howard Hughes Medical Institute and Harvard Medical School, Boston, MA, 02115, USA
SO J. Clin. Invest. (1999), 104(9), 1235-1244
CODEN: JCINAO; ISSN: 0021-9738
PB American Society for Clinical Investigation
DT Journal
LA English
AB To elucidate the role of **cardiac** myosin-binding protein-C (MyBP-C) in myocardial structure and function, we have produced mice expressing altered forms of this sarcomere protein. The engineered mutations encode truncated forms of MyBP-C in which the **cardiac** myosin heavy chain-binding and **titin**-binding domain has been replaced with novel amino acid residues. Analogous heterozygous defects in humans cause hypertrophic **cardiomyopathy**. Mice that are homozygous for the mutated MyBP-C alleles express less than 10% of truncated protein in M-bands of otherwise normal sarcomeres. Homozygous mice bearing mutated MyBP-C alleles are viable but exhibit neonatal onset of a progressive dilated **cardiomyopathy** with prominent histopathol. of myocyte hypertrophy, myofibrillar disarray, fibrosis, and dystrophic calcification. Echocardiog. of homozygous mutant mice showed left ventricular dilation and reduced contractile function at birth; myocardial hypertrophy increased as the animals matured. Left-ventricular pressure-vol. analyses in adult homozygous mutant mice demonstrated depressed systolic contractility with diastolic dysfunction. These data revise our understanding of the role that MyBP-C plays in

myofibrillogenesis during **cardiac** development and indicate the importance of the protein for long-term sarcomere function and normal **cardiac** morphol. We also propose that mice bearing homozygous familial hypertrophic **cardiomyopathy**-causing mutations may provide useful tools for predicting the severity of disease that these mutations will cause in humans.

RE.CNT 36
RE
(2) Bennett, P; J Muscle Res Cell Motil 1986, V7, P550 CAPLUS
(3) Bonne, G; Circ Res 1998, V83, P580 CAPLUS
(4) Bonne, G; Nat Genet 1995, V11, P438 CAPLUS
(5) Carrier, L; Circ Res 1997, V80, P427 CAPLUS
(7) Dennis, J; J Cell Biol 1984, V98, P1514 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 3 OF 12 CAPLUS COPYRIGHT 2001 ACS
AN 1999:538422 CAPLUS
DN 131:298226
TI Structural Analysis of the **Titin** Gene in Hypertrophic **Cardiomyopathy**: Identification of a Novel Disease Gene
AU Satoh, Manatsu; Takahashi, Megumi; Sakamoto, Tsuguya; Hiroe, Michiaki; Marumo, Fumiaki; Kimura, Akinori
CS Second Department of Internal Medicine, Tokyo Medical and Dental University, Tokyo, 113-8519, Japan
SO Biochem. Biophys. Res. Commun. (1999), 262(2), 411-417
CODEN: BBRCA9; ISSN: 0006-291X
PB Academic Press
DT Journal
LA English
AB Hypertrophic **cardiomyopathy** (HCM) is characterized by ventricular hypertrophy accompanied by myofibrillar disarrays. Mol. genetic analyses have revealed that mutations in 8 different genes cause HCM. Mutations in these disease genes, however, could be found in about half of HCM patients, suggesting that there are other unknown disease gene(s). Because the known disease genes encode sarcomeric proteins expressed in the **cardiac** muscle, we searched for a disease-assocd. **mutation** in the **titin** gene in 82 HCM patients who had no **mutation** in the known disease genes. A G to T transversion in codon 740, from CGC to CTC, replacing Arginine with Leucine was found in a patient. This **mutation** was not found in more than 500 normal chromosomes and increased the binding affinity of **titin** to .alpha.-actinin in the yeast two-hybrid assay. These observations suggest that the **titin mutation** may cause HCM in this patient via altered affinity to .alpha.-actinin. (c) 1999 Academic Press.

RE.CNT 39
RE
(1) Ayme-Southgate, A; Proc Natl Acad Sci USA 1991, V88, P7973 CAPLUS
(2) Bejsovec, A; Cell 1990, V60, P133 CAPLUS
(3) Benian, G; Genetics 1993, V134, P1097 CAPLUS
(4) Benian, G; Nature 1989, V342, P45 CAPLUS
(5) Bing, W; Biochem Biophys Res Commun 1997, V236, P760 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 4 OF 12 CAPLUS COPYRIGHT 2001 ACS
AN 1999:180566 CAPLUS
DN 131:68917
TI Familial dilated **cardiomyopathy** locus maps to chromosome 2q31
AU Siu, Benjamin L.; Niimura, Hideshi; Osborne, John A.; Fatkin, Diane; MacRae, Calum; Solomon, Scott; Benson, D. Woodrow; Seidman, J. G.; Seidman, Christine E.
CS Department of Pediatric Cardiology, Boston Children's Hospital, Boston, MA, USA
SO Circulation (1999), 99(8), 1022-1026
CODEN: CIRCAZ; ISSN: 0009-7322

PB Lippincott Willi[redacted] & Wilkins
DT Journal
LA English
AB Inherited gene defects are an important cause of dilated **cardiomyopathy**. Although the chromosome locations of some defects and 1 disease gene (actin) have been identified, the genetic etiologies of most cases of familial dilated **cardiomyopathy** remain unknown. The authors clin. evaluated 3 generations of a kindred with autosomal dominant transmission of dilated **cardiomyopathy**. Nine surviving and affected individuals had early-onset disease (ventricular chamber dilation during the teenage years and congestive **heart** failure during the third decade of life). The disease was nonpenetrant in 2 obligate carriers. To identify the causal gene defect, linkage studies were performed. A new dilated **cardiomyopathy** locus was identified on chromosome 2 between loci GCG and D2S72 (max. logarithm of odds [LOD] score=4.86 at .theta.=0). Because the massive gene encoding **titin**, a cytoskeletal muscle protein, resides in this disease interval, sequences encoding 900 amino acid residues of the **cardiac**-specific (N2-B) domain were analyzed. Five sequence variants were identified, but none segregated with disease in this family.
A dilated **cardiomyopathy** locus (designated CMD1G) is located on chromosome 2q31 and causes early-onset congestive **heart** failure. Although **titin** remains an intriguing candidate gene for this disorder, a disease-causing **mutation** is not present in its **cardiac**-specific N2-B domain.
RE.CNT 21
RE
(1) Arber, S; Cell 1997, V88, P393 CAPLUS
(2) Bowles, K; J Clin Invest 1996, V98, P1355 CAPLUS
(4) Bristow, M; J Clin Invest 1993, V92, P2737 CAPLUS
(6) D'Angelo, D; Proc Natl Acad Sci U S A 1997, V94, P8121 CAPLUS
(8) Hein, S; J Mol Cell Cardiol 1994, V26, P1291 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 5 OF 12 CAPLUS COPYRIGHT 2001 ACS
AN 1998:362696 CAPLUS
DN 129:120720
TI **Cardiac** myosin-binding protein C and hypertrophic **cardiomyopathy**
AU Carrier, Lucie; Bonne, Gisele; Schwartz, Ketty
CS Institutde Myologie, INSERM UR153, Groupe Hospitalier Pitie-Salpetriere, Paris, 75651, Fr.
SO Trends Cardiovasc. Med. (1998), 8(4), 151-157
CODEN: TCMDEQ; ISSN: 1050-1738
PB Elsevier Science Inc.
DT Journal; General Review
LA English
AB A review, with 51 refs. The **cardiac** myosin-binding protein C (MyBP-C) is a sarcomeric protein belonging to the intracellular Ig superfamily; it has both structural and regulatory roles. The gene-encoding **cardiac** MyBP-C in humans is located on chromosome 11p11.2, comprises over 21,000 base pairs, and contains 35 exons. Mutations have been identified in this gene in unrelated families with familial hypertrophic **cardiomyopathy**. Familial hypertrophic **cardiomyopathy** is an autosomal dominant disease characterized by ventricular hypertrophy assocd. with a large degree of myocardial and myofibrillar disarry. Most mutations found in the **cardiac** MyBP-C gene thus far are predicted to lead to an altered mRNA sequence and to produce the C-terminal truncation of the **cardiac** MyBP-C polypeptides lacking the myosin-binding site and also, in some cases, the **titin**-binding site. One might reasonably assume that the **cardiac** MyBP-C mutations exert their effect by altering the

multimeric comple[redacted]assembly of the **cardiac** sarcom[redacted] via the "null allele" me[redacted]hism, potentially leading to ha[redacted]oinsufficiency, and/or via a dominant neg. effect of a misfolded RNA on the **cardiac** MyBP-C translation, which could interfere with the proper assembly of sarcomeric structures. These data underline the functional importance of MyBP-C in the regulation of **cardiac** work and provide the basis for further studies and for the prodn. of transgenic animals for **cardiac** MyBP-C that will, one hopes, help to resolve the pathogenesis of chromosome-11-assocd. familial hypertrophic **cardiomyopathy**.

L8 ANSWER 6 OF 12 CAPLUS COPYRIGHT 2001 ACS
AN 1998:231921 CAPLUS
DN 129:36983
TI Identification of a new missense **mutation** in MyBP-C associated with hypertrophic **cardiomyopathy**
AU Moolman-Smook, Johanna C.; Mayosi, Bongani; Brink, Paul; Corfield, Valerie A.
CS Dept. of Medical Physiology and Biochemistry, Univ. of Stellenbosch and South African Medical Res. Council Centre for Molecular and Cellular Biology, Tygerberg, S. Afr.
SO J. Med. Genet. (1998), 35(3), 253-254
CODEN: JMDGAE; ISSN: 0022-2593
PB BMJ Publishing Group
DT Journal
LA English
AB Hypertrophic **cardiomyopathy** is a primary **cardiac** disease, characterized by idiopathic myocardial hypertrophy, and is caused by defects in sarcomeric protein encoding genes. One of these genes is **cardiac** myosin binding protein C (MyBP-C), in which a no. of splice site and duplication mutations causing HCM have been described. During **mutation** screening of a South African HCM population by PCR-SSCP, a missense **mutation**, Arg654His, was detected in one proband. Although the **mutation** was present in his three adult children, only the proband himself was markedly affected. This is the first report of a disease assocd. missense **mutation** in MyBP-C which does not affect the myosin or **titin** binding domains.

L8 ANSWER 7 OF 12 CAPLUS COPYRIGHT 2001 ACS
AN 1997:476634 CAPLUS
DN 127:186398
TI Novel splice donor site **mutation** in the **cardiac** myosin-binding protein-C gene in familial hypertrophic **cardiomyopathy**: characterization of **cardiac** transcript and protein
AU Rottbauer, Wolfgang; Gautel, Mathias; Zehelein, Jorg; Labeit, Siegfried; Franz, Wolfgang M.; Fischer, Christine; Vollrath, Benedikt; Mall, Gerhard; Dietz, Reiner; Kubler, Wolfgang; Katus, Hugo A.
CS Med. Klinik III, Univ. Heidelberg, Heidelberg, D-69115, Germany
SO J. Clin. Invest. (1997), 100(2), 475-482
CODEN: JCINAO; ISSN: 0021-9738
PB Rockefeller University Press
DT Journal
LA English
AB Familial hypertrophic **cardiomyopathy** is a disease generally believed to be caused by mutations in sarcomeric proteins. In a family with hypertrophic **cardiomyopathy** linked to polymorphic markers on chromosome 11, we found a new **mutation** of a splice donor site of the **cardiac** myosin-binding protein-C gene. This **mutation** causes the skipping of the assocd. exon in mRNA from lymphocytes and myocardium. Skipping of the exon with a consecutive

reading frame shift leads to premature termination of translation and is thus expected to produce a truncated **cardiac** myosin-binding protein-C with loss of the myosin- and **titin**-binding COOH terminus. However, Western blot anal. of endomyocardial biopsies from histol. affected left ventricular myocardium failed to show the expected truncated protein. These data show for the first time that a splice donor site **mutation** in the myosin-binding protein-C gene is transcribed to **cardiac** mRNA. Truncated **cardiac** myosin-binding protein-C does not act as a "poison polypeptide," since it seems not to be incorporated into the sarcomere in significant amts. The absence of mutant protein and of significantly reduced amts. of wild-type protein in the presence of the mutated mRNA argues against the "poison protein" and the "null allele" hypotheses and suggests yet unknown mechanisms relevant to the genesis of chromosome-11-assocd. familial hypertrophic **cardiomyopathy**.

L8 ANSWER 8 OF 12 MEDLINE
AN 2000266878 MEDLINE
DN 20266878
TI [Genetic changes and clinical management in familial hypertrophic **cardiomyopathy** [editorial].
Zmiany genetyczne a obraz kliniczny rodzinnej kardiomiopatii przerostowej.
AU Domal-Kwiatkowska D; Smolik S; Mazurek U; Moric E; Polonska J; Nowalany-Kozielska E; Glanowska G; Wodniecki J; Szarek J; Wilczewski P; Kozakiewicz K; Tendera M; Wilczok T
SO WIADOMOSCI LEKARSKIE, (2000) 53 (1-2) 4-21. Ref: 81
Journal code: XOA. ISSN: 0043-5147.
CY Poland
DT Editorial
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA Polish
EM 200009
EW 20000903
AB Hypertrophic **cardiomyopathy** (HCM) is phenotypically and genotypically heterogeneous disease of **heart**. Nine chromosomal loci responsible for this condition have been identified: beta-myosin heavy chain, essential and regulatory myosin light chains, troponin T and I subunits, alpha-tropomosin, **cardiac** myosin binding protein C, **cardiac** actin and **titin**. These genes code for proteins involved in the contraction mechanism or in the control of contraction, therefore HCM has been classified as a disease of **cardiac** sarcomere. Over 107 mutations have been identified. More then half of them have been detected in the beta-myosin heavy chain gene (beta-MHC). Some mutations in beta-MHC gene are associated with a benign prognosis, other are associated with high incidence of sudden **cardiac** death (SCD) and severe hypertrophy. Mutations in myosin binding protein C are associated with mild, delayed expression of **cardiac** hypertrophy and benign prognosis. Mutations in **cardiac** troponinT are associated with a mild degree of hypertrophy but a high incidence of SCD. Study of genes responsible for HCM will assume role in the context of clinical management of HCM, in particular regarding diagnosis and prognosis patients and families with HCM.

L8 ANSWER 9 OF 12 MEDLINE
AN 1998338775 MEDLINE
DN 98338775
TI Tibial muscular dystrophy--from clinical description to linkage on chromosome 2q31.
AU Udd B; Haravuori H; Kalimo H; Partanen J; Pulkkinen L; Paetau A; Peltonen L; Somer H
CS Neurological Department, Vasa Central Hospital, Finland..

bjarne.udd@walli[redacted]wasa.fi
SO NEUROMUSCULAR D[redacted]RDERS, (1998 Jun) 8 (5) 327-32.[redacted]
Journal code: BJS. ISSN: 0960-8966.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199812
AB A genome scan with highly polymorphic markers has established linkage for tibial muscular dystrophy (TMD), a recently described late onset distal myopathy, to a novel myopathy locus on chromosome 2q31. The mode of inheritance in TMD is autosomal dominant and the typical symptom of ankle dorsiflexion weakness appears in the fourth to seventh decade. Weakness of lower leg muscles is slowly progressive eventually causing a moderate foot drop. Overall disability usually remains mild even in elderly patients and walking ability is preserved throughout the patient's lifetime. The main target of the disease, the tibial anterior muscle, shows progressive dystrophic changes with rimmed vacuoles at the early stages and complete replacement pathology at later stages of the disease. The linkage studies in four different TMD families revealed a common core haplotype with a set of markers on the chromosome 2q31 locus. This indicates one major ancient founder **mutation** for TMD in Finland. There is one superior candidate gene on the 2q31 locus, the gene encoding a giant protein **titin**, expressed in **heart** and skeletal muscle.

L8 ANSWER 10 OF 12 MEDLINE
AN 96083592 MEDLINE
DN 96083592
TI Mutations in the **cardiac** myosin binding protein-C gene on chromosome 11 cause familial hypertrophic **cardiomyopathy**.
AU Watkins H; Conner D; Thierfelder L; Jarcho J A; MacRae C; McKenna W J; Maron B J; Seidman J G; Seidman C E
CS Howard Hughes Medical Institute, Boston, Massachusetts 02115, USA.
SO NATURE GENETICS, (1995 Dec) 11 (4) 434-7.
Journal code: BRO. ISSN: 1061-4036.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-S80805
EM 199603
AB Familial hypertrophic **cardiomyopathy** (FHC) is an autosomal dominant disorder manifesting as **cardiac** hypertrophy with myocyte disarray and an increased risk of sudden death. Mutations in five different loci cause FHC and 3 disease genes have been identified: beta **cardiac** myosin heavy chain, alpha tropomyosin and **cardiac** troponin T. Because these genes encode contractile proteins, other FHC loci are predicted also to encode sarcomere components. Two further FHC loci have been mapped to chromosomes 11p13-q13 (CMH4, ref. 6) and 7q3 (ref. 7). The gene encoding the **cardiac** isoform of myosin binding protein-C (**cardiac** MyBP-C) has recently been assigned to chromosome 11p11.2 and proposed as a candidate FHC gene. **Cardiac** MyBP-C is arrayed transversely in sarcomere A-bands and binds myosin heavy chain in thick filaments and **titin** in elastic filaments. Phosphorylation of MyBP-C appears to modulate contraction. We report that **cardiac** MyBP-C is genetically linked to CMH4 and demonstrate a splice donor **mutation** in one family with FHC and a duplication **mutation** in a second. Both mutations are predicted to disrupt the high affinity, C-terminal, myosin-binding domain of **cardiac** MyBP-C. These findings define **cardiac** MyBP-C mutations as the

cause of FHC on omosome 11p and reaffirm that is a disease of the sarcomere.

L8 ANSWER 11 OF 12 USPATFULL
AN 2000:105651 USPATFULL
TI Double-muscling in mammals
IN Grobet, Luc, Esneux, Belgium
Georges, Michel, Villers-aux-Tours, Belgium
PA University of Liege, Liege, Belgium (non-U.S. corporation)
PI US 6103466 20000815
AI US 1997-891789 19970714 (8)
DT Utility
EXNAM Primary Examiner: Fredman, Jeffrey
LREP Hunt, John C.
CLMN Number of Claims: 45
ECL Exemplary Claim: 1
DRWN 3 Drawing Figure(s); 3 Drawing Page(s)
LN.CNT 2353
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A gene (cDNA) encoding a bovine myostatin protein. The nucleic acid coding sequence is identified as SEQ ID NO:1 and the protein sequence is
identified as SEQ ID NO:2. A mutant gene (SEQ ID NO:3) in which the coding sequence lacks an 11-base pair consecutive sequence (SEQ ID NO:11) of the sequence encoding bovine protein having myostatin activity
has been sequenced. It has been shown that cattle of the Belgian Blue breed homozygous for the mutant gene lacking myostatin activity are double-muscled. A method for determining the presence of muscular hyperplasia in a mammal is described. The method includes obtaining a sample of material containing DNA from the mammal and ascertaining whether a sequence of the DNA encoding (a) a protein having biological activity of myostatin, is present, and whether a sequence of the DNA encoding (b) an allelic protein lacking the activity of (a), is present.
The absence of (a) and the presence of (b) indicates the presence of muscular hyperplasia in the mammal.

L8 ANSWER 12 OF 12 USPATFULL
AN 2000:18280 USPATFULL
TI Nucleic acid sequence of senescence asssociated gene
IN Funk, Walter, Hayward, CA, United States
PA Geron Corporation, Menlo Park, CA, United States (U.S. corporation)
PI US 6025194 20000215
AI US 1997-974180 19971119 (8)
DT Utility
EXNAM Primary Examiner: Huff, Sheela; Assistant Examiner: Bansal, Geetha P.
LREP Earp, David J.; Kaster, Kevin
CLMN Number of Claims: 10
ECL Exemplary Claim: 1,6
DRWN No Drawings
LN.CNT 4667
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Human gene GC6 is expressed more abundantly in senescent cells than young cells. Isolated, purified, and recombinant nucleic acids and proteins corresponding to the human GC6 gene and its mRNA and protein products, as well as peptides and antibodies corresponding to the GC6 protein can be used to identify senescent cells, distinguish between senescent and young cells, identify agents that alter senescent gene expression generally and GC6 expression specifically; such agents as well as GC6 gene and gene products and products corresponding thereto can be used to prevent and treat diseases and conditions relating to cell senescence.